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WO 03/082249 A1

(54) Title: CO-BEADLET OF DHA AND ROSEMARY AND METHODS OF USE

(57) Abstract: The present invention provides improved beadlet formulations useful for inclusion in dietary supplements customized for improving and maintaining ocular nutrition. In particular, the improved beadlets comprise DHA (docosahexaenoic acid); rosemary and/or its components; and excipients.

CO-BEADLET OF DHA AND ROSEMARY AND METHODS OF USE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the field of nutraceuticals and to the use of dietary supplements to maintain or improve ocular health.

2. Description of the Related Art

Dietary supplements are recommended for a variety of reasons including the improvement of vision or prophylaxis of vision loss. An example of dietary supplements useful in improving ocular nutrition and promoting healthy eyes are the ICaps® Dietary Supplements (Alcon Laboratories, Inc., Fort Worth, TX). Dietary supplements are generally consumed in the form of powders, tablets, capsules or gel-caps and comprise a variety of vitamins, minerals, and herbal or other organic constituents. Some dietary supplements are formulated with beadlets, which may function as carriers for the nutritional ingredients and may be blended and compressed into tablets or filled into capsules or gel caps.

Beadlets which contain dietary substances are generally small spheroids of less than about a millimeter in diameter. There are a variety of functions and purposes of beadlets. For example, beadlets may provide for the separate confinement (internal) and segregation from complementary (external) ingredients within the dietary supplement. This type of separation can isolate those components with the potential for interaction or reaction and thereby improve the stability and/or the availability of either entrapped or complementary external ingredients. The ingredients may be combined into a beadlet with a

complementary component which facilitates digestion or absorption improving bioavailability. More generally, the food industry has utilized microencapsulation to control availability, flavor, or odor and shelf-life and dosage uniformity stability of acidulants, aromas, nutritional oils and supplements, vitamins, minerals, dietary fibers, or leavening agents, and control of moisture, bacterial growth, and bioburden. The chemical industry has utilized the technology for numerous applications from controlling reaction rates to controlling distribution.

Various beadlet compositions are known and can be obtained from a number of food ingredient or supplement manufacturers, chemical or pharmaceutical manufacturers, specialized manufacturers, biotechnology companies and research institutes; and from independent university laboratories. Particular beadlet compositions for nutritional applications have been the subject of numerous patents including U.S. Patent Nos. 4,254,100 (Keller et al.) and 3,998,753 (Antoshkiw et al.). Methods of beadlet manufacture have been disclosed in U.S. Patent Nos. 4,670,247 (Scialpi) and 3,998,753.

Microencapsulation can be accomplished in one of several manners, from a simple capsular reservoir in which a particle, like an oil droplet, is coated with a thin, generally polymeric, coating to a monolithic matrix in which a final porous, commonly polymeric, structure is generated that can accommodate an active component in its interstices. In some instances, such as the technology to be claimed, it has been necessary to combine the two technologies, providing a coated monolithic active carrier.

Current beadlet compositions used in dietary supplements generally are restricted to the use of inert food-grade ingredients and excipients determined to be safe and effective and complementary to a single nutritional compound. In other instances, when molecules of the same class are refined from a particular source, for example a major component with

a minor related constituent, and both compounds produce parallel effects, such molecules may not necessarily be isolated but mixed together in a beadlet. These may be considered pseudo-single-component beadlets, and there are examples in the market place, e.g., Lutrinol® and FloraGLO® beadlets, which are a combination of lutein and zeaxanthin as formulated in Retoxil® Dietary Supplements. Examples of ingredients benefiting from beadlet confinement have included natural vitamins such as Vitamins A, D, E, and K; minerals such as iron and sodium bicarbonate; xanthophylls such as lutein, zeaxanthin, canthaxanthin, and astaxanthin; carotenoids and retinoid alone or in combination, , such as beta-carotene, lycopene, and retinol.

Pending U.S. patent application Serial No. 09/397,472 (the '472 application, herein incorporated by reference) and related foreign applications directed to beadlets containing more than one active ingredient. More specifically, those applications are directed to a beadlet containing one or more xanthophylls, one or more carotenes/retinoids, one or more antioxidants, and one or more solidifying agents. The beadlets of the '472 application are aimed at treating or preventing mammalian diseases or disorders. The '472 application does not discuss the use of DHA or rosemary alone or in any combination.

The preferred form of administering such compositions is the tablet. Unfortunately, previous attempts to create a beadlet containing DHA and produce a tablet from the beadlets have resulted in a tablet with a prominent unpleasant marine odor. Further, it was found that the beadlets themselves, after a short period of time, developed an unpleasant marine odor. Thus, what is needed is a beadlet formulation that is both substantially odorless and stable, which does not deteriorate over the shelf life of the product and which can withstand the compressive forces associated with manufacture, and especially of tableting.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing improved beadlet formulations useful for inclusion in dietary supplements. In particular, the improved beadlets comprise DHA (docosahexaenoic acid); rosemary and/or its components; and excipients. The beadlets are particularly useful for incorporation in dietary supplements customized for improving and maintaining ocular nutrition.

The present invention is also directed to improved dietary supplements comprising the improved beadlets. Preferred dietary supplements have been formulated as an aid to ocular health. The present invention is also directed to methods of using the beadlets and dietary supplements for improving nutritional health. The methods of the present invention are particularly directed to the enhancement of ocular health and the prophylaxis of retinal disorders, including age-related macular degeneration.

The application of the beadlet technology of the present invention to dietary supplements provides, and facilitates development of, enhanced nutritional supplementation. Such technology may aid in increasing bioavailablity of the dietary substances and also provide ease in modifying compositions containing DHA and rosemary within the supplement. Such improvements are believed to be particularly useful in the enhancement of ocular nutrition and improved ocular health.

In certain preferred embodiments, the present invention provides a cobeadlet and/or its coating containing docosahexaenoic acid (DHA) and/or rosemary. The DHA will be present in the beadlet in a concentration of preferably from about 0.1% to about 50% and the rosemary will be present in the beadlet in a concentration of preferably from about 0.1% to about 50%. More preferably, the beadlet will contain a concentration of DHA of from about 7% to about 25% and a concentration of rosemary of from about 2% to about 20%.

The coating, which serves as a barrier to oxidation from the outside and to escape of odorous agents or their byproducts from the inside, generally consists of a physically or chemically crosslinked or associated polymer and excipients, and may also include an agent such as rosemary to mask odors or prevent chemical dergradation.

It will be understood by the skilled artisan that the percentage ranges above (i.e., 0.1% to 50%, etc.) include all points in between said range. That is, it includes 0.2%, 0.3%, 0.4% and so on, 1.0%, 1.1%, 1.2% and so on, 5.0%, 5.1%, 5.2% ... 5.7%, 5.8%, 5.9% and so on up to and including 20%, 25%, 30%, 40%, etc.

The beadlets of the invention are virtually odorless. As used herein, the term "odorless" means that the beadlets of the invention have virtually no odor. Depending on the sensitivity of the nose, of course, some may detect no odor, some may detect a slight odor, and some may detect more than a slight odor. The term odorless as used herein is not meant to require that all beadlets are completely without odor but to require that the beadlets are substantially without odor. That is, the odor is substantially diminished compared to beadlets not having the combination of DHA and rosemary of the present invention.

The DHA for use in the beadlets of the present invention may come from fish oil or from fermentation of algae, but could also be derived from flaxseed or soybean or canola oil, borage, eggs or organ meats.. Most preferably, the DHA for use in the beadlets of the present invention is without any significant initial odor, *e.g.* that from fermentation of algae.

The beadlets of the invention may be in the form of capsular reservoir or monolithic matrix. Capsular reservoirs for an oily active, such as those of the current invention, typically consist of at least one surface-active agent, such as phospholipids and water-soluble polymers, utilized to stabilize microparticles of the active agent(s) suspended in a medium in which they do not dissolve. The coating may be any film-forming type of

coating material, such as carbohydrates (acacia and cellulose derivatives and dextrans to gelatin), gluten, polyesters, starch, lactide-glycolide copolymers, waxes, *etc.* One of skill in the art may easily select appropriate coatings based on their properties and their compatibility with the active component(s) and selected/required excipients.

Monolithic matrices essentially trap the active agent(s) within a "web" of polymer. While the monolithic matrix may be formed using any known method, it will generally be formed by precipitation polymerization, coacervation of polymeric blends, condensation polymerization, or by simple drying. In certain embodiments, the core of the carrier may comprise a monolithic matrix while the remainder of the beadlet is a capsular reservoir. In a preferred aspect, the core may be generated with acrylates.

The matrix may be loaded with active agent(s) either before or after polymerization. Whether loading occurs before or after polymerization will depend on the nature of the active agent(s) and/or upon the capacity of the carrier. Such determinations are well within the knowledge and the skill of the ordinary skilled artisan.

In addition, either type of microparticle may require other excipients such as plasticizers, dispersants, colorants and/or opaquants, extenders, and fillers.

Further, where the active agent(s) are unstable it may be further desirable to combine the capsular reservoir and matrix technologies. That is, the active agent(s) may be embeded within a matrix and then the matrix coated to restrict transport of degradizer into the core. This embodiment is preferred where one or more of the active agents are antioxidants. In certain preferred aspects, protective antioxidants can be placed in the core to protect the most vulnerable specie, and may also be placed in the coating. Such a coating can serve two purposes: first, the coating isolates the active and may reduce the rate at which reactive oxygen reaches the active embedded in the core; and second, the antioxidant in the coating

serves to reduce the limited amount of oxygen in the head space of the container, generally a plastic bottle of tablets or capsules.

Preferably, the cobeadlet of the invention will include the following components: two or more active agents; crystallizing or solidifying components, which may include active agents; polymers, either synthetic or biopolymeric; precipitating coacervating components; fillers, which may be inert components, may impart important physical properties to the beadlet, such as hardness or size characteristics, or may provide important chemical characteristics important to one or both of the actives, such as binding or stabilizing characteristics; plasticizers, which prevent the beadlet from being too fragile and crumbling during processing; and chemical agents which protect one or more of the active agents, improving their stability.

The present invention further provides a method of maintaining or improving ocular health in a mammal. The method of the invention generally includes administering to a mammal a composition comprising co-beadlets, wherein said co-beadlets comprise DHA and rosemary. In preferred embodiments, the beadlets for use in the methods of the invention will be as described above. Typically, the composition for use in the methods of the invention can be administered in many forms, including powder, capsule, caplet, gel cap or tablet. Most preferably, the composition will be administered in the form of a tablet, a tablet also intended to deliver other micronutrients of value in maintaining ocular nutrition.

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

The present invention is directed to improved beadlet formulations, improved dietary supplement formulations comprising the improved beadlets and methods of use. As used herein, "dietary supplement(s)" or the shortened form, "supplement(s)," refer to any finished, dietary supplement dosage form containing dietary substances and suitable for ingestion by a host, e.g., human or other mammal.

Docosahexaenoic acid (DHA) is an ω-3 essential fatty acid derived from fish oil or by fermentation, such as from algae. Both minor components of DHA and the by-products of its oxidation have been observed to possess an objectionable aroma, sometimes described as a "marine odor." Producers have attempted to eliminate this drawback of the use of DHA by devising a purer product, by creating carriers capable of protecting the product from oxidation, by masking the odor with a more acceptable fragrance (*e.g.*, a citrus fragrance), or a combination of these technologies. For example, both the fermentation process and the isolation of the DHA from the broth have been improved. The result has been a DHA product that has significantly diminished marine odor relative to that obtained from fish oil.

To improve stability of that product and maintain the more odor-free status, the DHA was encapsulated in a beadlet. In one form, the beadlet was produced using gelatin beadlet technology. The beadleted DHA was then formed into a tableted product. When the DHA-containing beadlets were compared with DHA-containing beadlets manufactured using fish-oil derived DHA, a significant improvement in the odor was detected. However, when the beadlets were made into tablets, the marine odor was prevalent, regardless of the source of the DHA. The marine odor was found to increase with time.

Initial studies of tableted formulations of DHA oil indicated that in order to control the dominant marine odor emanating from the tablets, it would be necessary to encapsulate

this ω-3 fatty acid. Algal DHA possessed a less offensive odor than that derived from fish oil, and beadlets of the algal DHA were least offensive. However, following tableting, some of the offensive odor was regenerated. An analagous instability had been observed with the compression of lutein beadlets ... only after compression were they observed to be unstable. It is believed that the effect of compression was to expose an increasing fraction of the compound to oxidation. The compression of the DHA beadlets to produce tablets appeared to produce a similar effect; namely, that compression was allowing an increasing fraction of the DHA to be exposed to oxidation, and that it was the oxidized ('rancid') product that generated the more offensive odor. Thus, the present inventor conceived that an antioxidant in sufficient concentration might serve to protect, or assist in protecting, beadletted DHA exposed to the pressure of tablet compression.

It was known that including antioxidants safe for human consumption, such as tocopherols (vitamin E-related compounds) and ascorbates (vitamin C derivatives), in beadlets with lutein protected the lutein from oxidation. Without being bound to any theory, it is believed that the antioxidants protect the lutein by behaving in specific ways: (1) all of the oxygen in the head space eventually reacts with antioxidants; (2) any oxygen which diffuses through the plastic bottle also will react with the confined antioxidants; (3) the oxygen reacts more rapidly with the most oxidizable antioxidants. Thus, the antioxidants in the beadlets are "used up" before oxidization can effect the more important active ingredient. While the DHA has been found to be protected by the rapidly oxidizable components in rosemary, other sources of even more rapidly oxidizable concentrated botanically derived antioxidant are anticipated to provide comparable benefit and are envisioned to be encompassed by the claimed technology.

The present inventor has found that some antioxidants, namely vitamins C and E and rosemary, are effective in protecting retinas from acute light-induced toxicity. Cellular antioxidants function in a cascade of reactions in order to protect sensitive organelles against reactive oxygen species in metabilizing tissues, in which oxygen eventually is reduced to water. For example, ascorbate is known to regenerate the reduced specie of Vitamin E from the oxidized specie. Therefore, the present inventor conceived that rosemary in sufficient quantities in a co-beadlet with DHA might serve multiple purposes. First, it acts as a second active ingredient, providing protection for the eyes and improving ocular health. Second, it acts as a "stabilizer," increasing shelf-life of the product. Finally, it acts as a "de-odorizer," masking the marine-odor of the DHA by preventing its oxidation, and imparting a favorably perceived fragrance.

The present inventor has found that adding rosemary and/or its components to DHA-containing beadlets, such that both "active" ingredients are present in a single beadlet, eliminates the off-odor associated with oxidized DHA while stabilizing the composition, thus increasing its shelf-life. It is contemplated that virtually any beadlet technology, such as that described in U.S. Patent Nos. 4,254,100; 3,998,753; 4,670,247; and 3,998,753 will be useful in the practice of the present invention.

Stability of the beadlet in the present context refers to good containing properties, i.e. the encapsulation protects the active compound(s) from exposure to oxidation and other conditions which may adversely affect the compound or its subsequent availability. The rosemary within the same beadlet as the DHA provides even further protection of the DHA from oxidation and other conditions which may cause the production of the characteristic unpleasant "marine" odor, and contributes to its value as an ocular nutrient.

According to a particular embodiment of the present invention, the microencapsulated DHA/rosemary-containing composition contains 0.1% to 40% of DHA, wherein the particle size of the DHA/rosemary beadlets range from about 100 μm to about 600 μm, though occasional large particles up to 800 μm and small fines of as small as 10 μm may be acceptable as well. The microencapsulated compositions of the present invention are suitable for tablet preparation, hard shell capsule filling and incorporating in different foods. According to a particular embodiment of the present invention, the DHA/rosemary mixtures employed herein may further comprise fillers, excipients or additives. Examples of suitable fillers include starch, pectins, carrageenans, xanthan gums, proteins, polyethylene glycols, cellulose derivatives (e.g., methyl cellulose, hydroxypropyl cellulose and ethyl cellulose) and other polysaccharides.

The present invention is advantageous in that it describes microcapsules, or beadlets, containing DHA and rosemary having virtually no offensive odor, with improved stability, relatively high content of the active agents and improved bioavailability of the active agents. The advantages of the claimed invention derive from the presence of the DHA/rosemary mixtures together in the same beadlet thus decreasing or eliminating offensive odors and increasing stability and shelf-life. The microcapsules of the present invention are tablet grade, i.e., suitable for use in tableting. Preferred compositions of the present invention are gelatin free.

The beadlets of the invention are capable of protecting the active agents (DHA and rosemary) from oxidative damage accompanying exposure to oxygen in the package headspace and/or transported across the package barrier during the shelf-life storage of the product. The beadlets of the invention are further capable of withstanding the compressive forces of 15 SCUor greater and preferably 20 SCU or greater occurring during tableting so

that the confined antioxidants of the final product are compromised neither in stability nor in efficacy.

The present invention additionaly provides a composition of the dosage form, containing both the beadlets with the properties defined above as well as other antioxidants themselves (which may or may not be confined in beadlets), such that the most oxidizable component, generally the antioxidants found in rosemary, is present in sufficient abundance to react and deactivate the oxygen in the head space, and protect all of the remaining antioxidants (carotenoids, xanthophylls, vitamins, other polyphenolics, *etc.*). The amount of rosemary in the body of the tablet (not included in the amount contained in / on the carrier beadlet [above]) generally will be greater than 3 mg / tablet and preferably greater than 5 mg / tablet when these tablets are packaged conventionally in bottles of 60 tablets and the container is LDPE or the equivalent in oxygen transmissability, and the protective antioxidant is *unfortified* rosemary oil. As will be well understood by those trained in the art, the amount may be reduced if concentrated forms of the reactive antioxidants in rosemary are utilized. The amount of rosemary in the body of the tablet preserves activity of all the tablet antioxidants, whereas the rosemary contained within the beadlets provides nutritional and therapeutic value, as well as stabilization for the beadlet.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which

are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Excipients for gelatin-based cobeadlets

In the following examples of the technology, actives and coactives refer to DHA and rosemary, or the components thereof. Specific examples of the technology include composition of the cobeadlets, composition of an optional coating, and ingredients and excipients contained in a complete tablet. Examples of cobeadlets include:

Core Coactives	15 %
Vegetable oil and Oleoresin	18.5 %
Hydrolyzed Gelatin	27.5 %
Sucrose	12 %
Ascorbyl Palmitate	3 %
Coating Rosemary (LycoRose)	3 %
Coating Corn Starch and cellulose	16 %
Water	5 %

Example 2

Excipients for nongelatin-based cobeadlets

Core Coactives:	24 %
Sodium alginate:	24.8 %
Isolated soy protein:	16.5 %
Silicon dioxide:	2 %
Coating Hydroxypropyl cellulose (Klucel)	14.5 %
Coating Herbalox type O (rosemary)	4.8 %
Lyc-o-rose (rosemary):	1.9 %
Ethoxylated glycerides:	4.8 %
Sucrose ester:	1.9 %
Water and Ca:	~5 %

Example 3

Examples of the coating technology

Excipients for a coating of cobeadlet cores, especially for a non-gelatin based core

Active or Coactives	3%
Hydroxypropylcellulose	16%
Methanol	30%
Acetone	51%

A. Excipients for a coating of cobeadlet cores, especially for a gelatin-based core

Active or Coactives	4%
Corn Starch	10%
Cellulosic	22%
Water	60%

Example 4

Examples of actives in tablet and capsule formulations

useful for maintaining ocular health

A. Actives in an ophthalmic formulation

Ingredient	Icaps Rev 3 Formula (per tablet)	Units
Vitamin A	2,500	IU
(β-carotene)	1.5	Mg
Vitamin B-2	5	Mg
Folate	100	µg
Vitamin B-12	3	µg
Vitamin C	200	Mg
Vitamin E	75	IU
Copper	0.5	Mg
Manganese	5	Mg
Selenium	20	µg
Zinc (acetate)	7.5	Mg
Lutein (max)	2	Mg
Zeaxanthin (min)	1	Mg
DHA (docosa-hexaenoic acid [22:6ω3])	5	Mg
Rosemary (minimum)	≤5	Mg

B. Actives & excipients (indented) in an ophthalmic formulation:

Ascorbic Acid
Gelatin
Hydroxypropyl Methylcellulose
dl-Alpha Tocopherol Acetate
Dicalcium Phosphate
Microcrystalline Cellulose
Magnesium Stearate
Sucrose
Silicon Dioxide
Zinc Acetate Dihydrate
Manganese Amino Acid Chelate
Corn Starch
Water
Sodium alginate
Selenium Amino Acid Chelate
Soy protein (isolated)
Titanium Dioxide
Hydroxypropyl cellulose (Klucel)
Fatty acids (DHA excipients)
DHA (in oil carrier)
Copper Amino Acid Chelate
Riboflavin
Polyethylene Glycol
Lutein / Zeaxanthin
Water and Ca
Ethoxylated glycerides
Ascorbyl Palmitate
Beta Carotene
Rosemary (from Herbalox type O)
Sodium Ascorbate
dl-Alpha Tocopherol
Zeaxanthin
Canola oil (Herbalox excipient)
Soybean oil (Herbalox excipient)
Excipients
Sorbic Acid
Polysorbate 80
Sodium Benzoate
Folic Acid
Vegetable oil (Lyc-o-Rose excipient)
Carnauba Wax
Cyanocobalamin

Example 5

Manufacture of tablets from the microcapsules described in Examples 1 and 2. The ingredients, all core actives and excipients including the cobeadleted DHA and rosemary, are blended and granulated to form a homogenous mass, which is stored in nearly full, low-headspace, sealed plastic bags. As quickly as possible, eliminating any significant delays, the blend is tableted to a hardness of approximately 22 SCU, and the tablets again stored in nearly full, low-headspace, sealed plastic bags until the tablets can be coated, a hiatus that will be kept to a minimum. The tablets are finally spray coated, dried, and packaged.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

United States Patents

3,998,753

4,254,100

4,670,247

We Claim:

1. A cobeadlet comprising docosahexaenoic acid (DHA) and rosemary.
2. The cobeadlet of claim 1, wherein said beadlet is odorless.
3. The cobeadlet of claim 1, wherein said DHA is obtained by fermentation from algae.
4. The cobeadlet of claim 1, further comprising at least one antioxidant other than rosemary.
5. The cobeadlet of claim 1, wherein the concentration of DHA is from about 0.1% to about 50% and the concentration of rosemary is from about 0.1% to about 50%.
6. The cobeadlet of claim 5, comprising from about 7 % to about 25% DHA and from about 2% to about 20% rosemary.
7. A method of maintaining or improving ocular health in a mammal, said method comprising administering to said mammal a composition comprising co-beadlets, wherein said co-beadlets comprise DHA and rosemary.
8. The method of claim 7, wherein said composition comprises from about 0.1% to about 50% DHA and about 0.1% to about 50% rosemary.
9. The method of claim 8, wherein the composition is in the form of a tablet.
10. A tablet comprising the cobeadlet of claim 1.
11. The tablet of claim 10, further comprising as excipients outside of the cobeadlets, at least 3 mg rosemary oil.
12. The tablet of claim 11, wherein the tablet comprises at least 5 mg rosemary oil.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/08558

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 465, 485, 486, 488, 489, 490, 492, 493, 494, 496, 497, 498

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST- search terms: dha, docosahexaenoic acid, rosemary, microcapsule, microsphere, beadlet, cobeadlet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,525,306 (YAJIMA) 25 June 1985, see claims 1-8.	1-12
Y	JP 10286079 A (K. MORITA) 27 October 1998, see page 1, abstract.	1-12
P, Y	US 6,444,242 B1 (SKELBAEK et al) 03 September 2002, see claims 1-19.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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Date of the actual completion of the international search	Date of mailing of the international search report
17 JUNE 2003	27 AUG 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-1235

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